REMARKS

Status of the Claims.

Claims 45-86 were pending in the application. Claims 45-61 and 68-76 are pending with entry of this amendment, claims 62-67 and 77-86 being cancelled.

Election/Restriction.

The Office Action confirms Applicants' position that the election of species is a Markush election. Office Action, page 1. However, the Examiner stated that "currently, no claim is completely generic," and indicated that "only claims 45, 46, 56, 58-61, 68-71 [and] 74-76 will be examined." *Id.*

Election of species practice relating to Markush claims is governed by M.P.E.P § 803.02, which states:

> This subsection deals with ***Markush-type generic claims*** which include a plurality of alternatively usable substances or members. In most cases, a recitation by enumeration is used because there is no appropriate or true generic language.

(Emphasis added.) Applicants respectfully point out that claims 45 and 68 are Markush-type generic claims that read on the elected species, chromosomal region 17q22-q24.

Section 803.02 states:

> ***Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection***, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, ***the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim***.

(Emphasis added.) In the present application, in response to the rejection of Markush-type claims, Applicants have overcome an obviousness-type double patenting rejection by filing a Terminal Disclaimer and have overcome a § 103 rejection by pointing out that the references doe not teach or suggest an amplification at 17q22-24 (see below). Therefore, Markush-type claims 45 and 68 must be reexaminined, and the prior art search must be extended to the extent necessary to determine the patentability of these claims. Applicants submit that § 803.02 requires the Examiner to examine at least one additional species recited in these claims. If the Examiner is able to make a proper art-based rejection of this additional species, the Examiner need not go on to examine any other species.

If the Examiner is not able to make such a rejection, the Examiner must go on to examine another additional species. Examination of the Markush claims must continue until the Examiner encounters a species that can properly be rejected over prior art or the Markush claims are fully examined. Accordingly, Applicants respectfully request examination of one or more of the additional species recited in claims 45 and 68, in compliance with § 803.02.

Obviousness-Type Double Patenting.

Claims 45, 46, 56, and 58-61 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-27 of U.S. Patent No. 5,721,098 in view of Bloomfield *et al.* (Cancer Res. (1983) 2975-84). Office Action, page 2. As the Examiner indicated, a "timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome [a] . . . rejection based on a nonstatutory double patenting ground." Enclosed is a Terminal Disclaimer over U.S. Patent No. 5,721, 098. Withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. § 103(a).

Claims 68-71 and 74-76 were rejected under 35 U.S.C. § 103(a) as allegedly obvious in light of Alitalo (Proc. Natl. Acad. Sci. USA(1983) 80:1707-11) in view of Hainsworth *et al.* (Cancer Genet. Cytogenet. (1991) 53:205-18). Office Action, page 3. This rejection is respectfully traversed.

Of the rejected claims, only claim 68 is independent. Claim 68 relates to a "method for detecting a copy number variation in a suspected breast cancer sample by detecting an amplification or gain of unique sequences at" positions including q22-q24 on chromosome 17. Detection is carried out by hybridizing a suitable probe to the sample and detecting the hybridization complex.

The Examiner stated that "Alitalo teaches a method for detecting an amplification of 8q24 comprising contacting a chromosome sample with a labeled nucleic acid probe which binds to 8q24 . . . [and] detecting the hybridization complex." Office Action, page 3. The Examiner further stated: "Hainsworth teaches that, at least in some instances, there is chromosomal gain at 17q23 in primary breast cancers (see table 2, case 907, where there is a derivative of chromosome 17 which is translocated in 17q23, which represents an amplification at that position)." *Id.*

As those skilled in the cytogenetics art readily appreciate, the terms "amplification" and "translocation" describe two distinct chromosomal or genetic abnormalities. For example, the background section of Applicants' specification states: "Chromosomal or genetic rearrangements include translocations (transfer of a piece from one chromosome to another chromosome), dicentrics (chromosomes with two centromeres), inversions (reversal in polarity of chromosomal segment), insertions, amplification and deletions." Applicants' specification, page 2, lines 17-23. Henderson's Dictionary of Biological Terms defines a translocation as a "chromosomal rearrangement in which part of a chromosome breaks off and is rejoined to a non-homologous chromosome." Henderson's Dictionary of Biological Terms 557 (Longman Group UK Limited 1989). The term "amplification," on the other hand, refers to the presence of additional copies of a nucleic acid sequence. Henderson's defines an amplification as "multiplication of a gene or DNA sequence." *Id.* at 24-25. Copies of the relevant pages of Henderson's are enclosed for the Examiner's convenience.

The Examiner contended that case 907 in Table 2 of Hainsworth discloses "a derivative of chromosome 17 which is translocated in 17q23, which represents an amplification at that position." Office Action, page 3. This table includes a column ("Clonal alterations") in which the chromosomal abnormalities observed in primary breast cancer cases are described. For case 907, the abnormalities are described as "del(11)(q22),t(7;16)(q22;q22),der(17)t(17;?)(q23;?),r(6)." The description of each distinct chromosomal abnormality is separated by commas. Thus, the abnormality of chromosome 17 is "der(17)t(17;?)(q23;?)." This "shorthand" would be interpreted by a cytogeneticist as describing a derivative of chromosome 17 that contained translocated chromosome 17 material joined to an unknown chromosome. The breakpoint on chromosome 17 is q23, and the chromosome 17 material is joined to an unknown point on the other chromosome. Nothing in this description would lead a cytogeneticist to conclude that any chromosome 17 sequences where amplified, much less those at q23. In addition, Table 2 shows that unidentified marker chromosomes were not observed in case 907. Unidentified chromosomes can sometimes contain amplified sequences, but no such chromosomes were found in case 907. Thus, there is simply no basis for the Examiner's assertion that the 17q23 translocation in case 907 "represents an amplification."

The cited references, taken singly or in combination, fail to teach or suggest "detecting an amplification or gain of unique sequences . . . on chromosome 17, [from] about position q22 to about position q24." Because the references fail to teach or suggest all of the

elements of claim 68, this claim is clearly patentable over the references. Claims 69-71 and 74-76 depend from claim 68 and are patentable over the cited references at least by virtue of this dependence. Accordingly, withdrawal of the rejection of claims 68-71 and 74-76 is respectfully requested.

Conclusion

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF USSN 09/912,818 WITH ENTRY OF THIS AMENDMENT

62-67. **(Canceled)**

77-86. **(Canceled)**

APPENDIX B

CLAIMS PENDING IN USSN 09/912,818 WITH ENTRY OF THIS AMENDMENT

45. (Amended) A method of detecting an amplification or gain of unique sequences at at least one chromosomal region selected from the group consisting of:

on human chromosome 1,
about position p22 to the centromere;
the q arm;
the centromere to about position p32;
about position q31 to qter;
about position q32;
about position q32 to qter;
on human chromosome 2,
the p arm;
on human chromosome 3,
about position p14;
about position p14 to qter;
about position p22 to pter;
about position q26 to qter;
on human chromosome 4,
the p arm;
about position q32 to about position q34;
on human chromosome 5,
the p arm;
about position q31 to qter;
about position q32 to qter;
on human chromosome 6,
the p arm;
the centromere to about position p21;
about position p23 to pter;
the centromere to about position q21;

about position q12 to about position q13;
about position q21;
about position q21 to about position q22;
on human chromosome 7,
the p arm;
the centromere to about position p12;
about position p21;
pter to about position q31;
the q arm;
about position q22 to about position q32;
on human chromosome 8,
about position p12;
the q arm;
about position q21;
about position q21 to about position q23;
about position q21 to qter;
about position q22 to about position q23;
about position q22 to qter;
about position q23 to about position q24;
about position q23 to qter;
about position q24;
on human chromosome 10,
the p arm;
the centromere to about position q21;
about position q22;
on chromosome 11,
about position p15;
the q arm;
about position q13;
on human chromosome 12,
the p arm;

the q arm;
about position q14 to about position q15;
about position q21;
about position q21 to about position q23;
about position q24;
on human chromosome 13,
about position 22 to qter;
about position q31 to qter;
on human chromosome 14,
the q arm;
about position q24 to qter;
about position q31;
about position q31 to qter;
on human chromosome 15,
about position q21 to qter;
about position q24;
about position q25;
about position q26;
entire human chromosome 16;
on human chromosome 16,
the p arm;
the q arm;
about position q23 to about position q24;
on human chromosome 17,
the centromere to about position q24;
about position q12;
about position q21 to qter;
about position q22 to about position q23;
about position q22 to about position q24;
about position q22 to qter;
about position q24 to qter;

on human chromosome 18,

the p arm;

on human chromosome 19,

the q arm;

about position q13;

about position q13 to qter;

entire human chromosome 20;

on human chromosome 20,

the p arm;

the q arm;

about position q12 to about position q13;

about position q13;

about position q13 to qter;

about position q34;

qter;

entire chromosome 21;

entire chromosome 22;

on the human X chromosome,

the p arm,

in a test sample, said method comprising:

(a) labelling nucleic acids from the test sample and from a control sample with different labels;

(b) contacting said labelled nucleic acids from each sample with a plurality of target nucleic acids, wherein either the labelled nucleic acids or the target nucleic acids, or both, have had repetitive sequences, if initially present, blocked and/or removed; and

(c) comparing the intensities of the signals from labelled nucleic acids hybridized to each target nucleic acid, thereby allowing detection of the presence or absence of the amplification or gain in the test sample.

46. The method of claim 45, wherein the step of comparing the intensities of the signals from the labelled nucleic acids comprises determining the ratio of the intensities of the signals as a function of position in the target nucleic acids.

47. The method of claim 45, wherein the amplification is of the q arm of human chromosome 1.

48. The method of claim 45, wherein the amplification is of the p arm of human chromosome 7.

49. The method of claim 45, wherein the amplification is of the q arm of human chromosome 8.

50. The method of claim 45, wherein the amplification is at about position q24 on human chromosome 8.

51. The method of claim 45, wherein the amplification is of the q arm of human chromosome 11.

52. The method of claim 45, wherein the amplification is at about position q13 on human chromosome 11.

53. The method of claim 45, wherein the amplification is of the q arm of human chromosome 12.

54. The method of claim 45, wherein the amplification is of the q arm of human chromosome 14.

55. The method of claim 45, wherein the amplification is of the q arm of human chromosome 16.

56. The method of claim 45, wherein the amplification is at about position q22 to about position q24 on human chromosome 17.

57. The method of claim 45, wherein the amplification is of the q arm of human chromosome 20.

58. The method of claim 45, wherein the target nucleic acids comprise at least one metaphase chromosome.

59. The method of claim 45, wherein said nucleic acid sample comprises genomic DNA molecules.

60. The method of claim 45, wherein said nucleic acid sample comprises DNA amplified from said test sample.

61. The method of claim 45, wherein said nucleic acid sample comprises complementary DNA.

68. A method for detecting a copy number variation in a suspected breast cancer sample by detecting an amplification or gain of unique sequences at at least one chromosomal region selected from the group consisting of:

on chromosome 17, about position q22 to about position q24;
on chromosome 20,
the q arm;
about position q13,
said method comprising:

(a) contacting a probe that binds selectively to a target polynucleotide sequence of said region with a nucleic acid sample prepared, directly or indirectly, from said suspected breast cancer sample, wherein said nucleic acid sample comprises said target polynucleotide sequence and said probe is contacted with said sample under conditions in which said probe forms a stable hybridization complex with said target nucleic acid sequence; and

(b) detecting said hybridization complex.

69. The method of claim 68, wherein said probe is labeled.

70. The method of claim 68, wherein said nucleic acid sample is labeled.

71. The method of claim 68, wherein the amplification is at about position q22 to about position q24 on human chromosome 17.

72. The method of claim 68, wherein the amplification is of the q arm of human chromosome 20.

73. The method of claim 68, wherein the amplification is at about position q13 on human chromosome 20.

74. The method of claim 68, wherein said nucleic acid sample comprises genomic DNA molecules.

75. The method of claim 68, wherein said nucleic acid sample comprises DNA amplified from said suspected breast cancer sample.

76. The method of claim 68, wherein said nucleic acid sample comprises complementary DNA.